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EXAMINER	
GOLLAMUDI, SHARMILA S	
ART UNIT	PAPER NUMBER
1616	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/28/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/886,296	TARARA ET AL.	
	Examiner	Art Unit	
	Sharmila S. Gollamudi	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-15,18-23,39,40,42-47 and 49-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-15, 18-23, 39-40, 42-47, and 49-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Request for Continued Examination filed 12/6/06 is acknowledged. Claims **4-15, 18-23, 39-40, 42-47, and 49-56** are pending in this application. Claims 1-3, 16-17, 24-38, 41, and 48 stand cancelled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 4-15, 18-23, 39-40, 42-47, 49-50, and 55-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5,855,913) in view of Unger (6,120,751).

Hanes et al teach aerodynamically light particles for drug delivery to the pulmonary system. The particles have a tap density of less than 0.4 g/cm3, aerodynamic diameter of 3 microns (see column 9, line 45-50), and a mass mean diameter (geometric diameter) between 5 to 30 microns. See abstract, See column 9, lines 26-45, and claim 1. Claim 3 teaches a tap density of less than 0.1 g/cm3. Table 2 teaches the porous microparticles with DPPC

(phospholipids) have a density of 0.30 g/cm3. It should be noted that Hanes teaches tap density is a standard measure of the envelope mass density (bulk density) on column 9, lines 5-6. On column 14, lines 36-40, Hanes teaches the bulk density is estimated by tap density measurements.

Hanes teaches the presence of irregular surface structure, or pores or cavities within the particle (this reads on instantly claimed "hollow microstructure") contributes to the aerodynamic lightness. Hanes also teaches the irregular surface texture and porous structure also contributes to the low tap density and manipulation of these features permits the delivery of larger particle envelope volumes into the lungs (col. 9, lines 10-25). Porosity and surface roughness can be increased by varying the inlet and outlet temperatures, among other factors. See column 12, lines 10-13. The aerodynamically light particles may be fabricated to provide a particle sample with a preselected size distribution. For example, greater than 30%, 50%, 70%, or 80% of the particles in a sample can have a geometric diameter within a selected range of at least 5 microns. The particles contain surfactants such as DPPC (instant gel to liquid temperature; see US 5,776,488 as art of interest) and the microstructures are taught to encapsulate active agents, which allows the active to remain protected (col. 10, lines 37-50 and examples). Note that DPPC is a zwitterionic lipid. The particles can also be co-delivered with larger carrier particles, not carrying a therapeutic agent, having, for example, a mean diameter ranging between about 50 microns and 100 microns. See column 4, lines 12-15.

Biodegradable polymer, copolymers, or a blend may be utilized. Hanes teaches the use of polyglycolic acid and polylactic acid with a surfactant (DPPC) may be utilized and the polyester may also have a charged or functionizable groups such as amino acids. Other polymers taught

are acrylic acids and methacrylic acids and polyvinyl compounds may be used to make the microsphere. See column 5, line 49 to column 6, line 27. Further, the particles may be formed into microspheres by methods such as coacervation, interfacial polymerization, etc. (note col. 6). Instant therapeutic agents including insulin, growth hormones, etc. are taught on column 10, lines 4-30.

Hanes teaches aerodynamically light PEG particles were prepared by spray drying using 5 g PEG (MW 15,000-20,000, Sigma) and the surfactant such as DPPC may be incorporated into the polymer solution prior to particle formation, or optionally the particles can be ionically or covalently coated by surfactant on the particle surface after particle formation, or the surfactant may be absorbed onto the particle surface. See column 13, lines 1-25.

Hanes et al do not teach the use of calcium in the structural matrix.

Unger teaches charged lipids and their use for drug delivery, targeted delivery, etc. See abstract. Unger teaches prior art studies have described the effects of calcium and other multivalent cations on membrane asymmetry, lipid distribution, vesicle size, aggregation and fusion. The general consensus exists that multivalent cations, such as calcium and magnesium, in the external environment of phospholipid vesicles cause the structures to aggregate into larger, multilamellar structures and promotes fusion. Unger's composition comprises a charged lipid, a counter ion, a lipid covalently bonded to a polymer, and a bioactive agent. See column 2, lines 20-30. The composition is in the form of a vesicle including liposomes and micelles, which can be solid or porous. See column 4, lines 19-45. The vesicles preferably have diameters of less than about 30 microns and more preferably less than about 12 microns. See column 68, lines 1-6. The charged lipid may be anionic (i.e., negatively charged, that is, carrying a net negative

charge) or cationic (i.e., positively charged, that is, carrying a net positive charge). See column 11, lines 5-10. A cationic counter ion is used to form the compositions. Preferred cations are **calcium**, magnesium, and zinc, and paramagnetic cations such as manganese and gadolinium. Most preferably the cation is calcium. See column 12, lines 1-5. Specifically, example 2 teaches the composition comprising instantly claimed dipalmitoylphosphatidylcholine (**DPPC**), dipalmitoylphosphatidic acid (DPPA), dipalmitoylphosphatidylethanolamine-polyethylene glycol-5,000 (DPPE-PEG5,000), and calcium chloride. Example 13 discloses lyophilizing the composition of example 2 to yield a dry powder. Unger teaches the lipid covalently bonded to a polymer (e.g., DPPE-PEG-5,000) causes compaction of the size of the composition in the presence of a counter ion, such as calcium, when compared to the corresponding compositions that do not contain a counter ion. The compaction effect caused by the lipid covalently bonded to the polymer is most notable when the counter ion is added at the initial incubation of the lipid mixture. Increasing the amount of the lipid covalently bonded to a polymer allows the composition to stabilize in the presence of a counter ion. When the lipid covalently bonded to the polymer is present in an amount less than about 5%, the composition is generally unstable and may precipitate. See column 10, lines 50-55. Unger discloses the lipid composition is useful for delivering bioactive agents to a patient's lungs. For pulmonary applications, dried or lyophilized powdered compositions are administered via an inhaler.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Unger and utilize calcium in the microstructures of Hanes. One would have been motivated to utilize calcium in the formation of Hanes's particles since Unger teaches the use of a cations such as calcium promotes fusion of the

phospholipids and stabilizes compaction of phospholipid-polymer containing particles, specifically in a PEG-phospholipid particle. Further, a skilled artisan would have expected the same stabilizing effect in Hanes's particles since Hanes also teaches a particle comprising PEG and a phospholipid.

With regard to the claims 4-5 (porosity), claims 6-7 (pore size), and claim 13 (shell thickness), although Hanes does not specify the porosity in terms of weight percent as instantly claimed, specify the pore size, or the shell thickness, it is the examiner's position that the Hanes would have a similar porosity, pore size, and shell thickness as instantly claimed for the following reason: Hanes teaches a substantially similar particle with instant bulk density (measured by tap density), instant geometric diameter, and instant aerodynamic diameter. Thus, "when a structure recited in the reference is substantially identical to that of the claims, claimed properties are presumed to be the inherent". See MPEP 2112.01. Further, Hanes teaches the porous and light nature of the microstructure contributes to the properties such as the low tap density of the particle and Hanes teaches the same density as claimed; thus the pore size and porosity must be similar as instantly claimed. Further, since the shell thickness also would contribute to the density of the particles and the prior art teaches the same density as claimed, it is the examiner's position that the prior art would have the same shell thickness as claimed. It should be noted that the examiner has provided a rationale as to why Hanes's particle would have the same or similar porosity, pore size, and shell thickness; thus the burden has shifted to the applicant to provide evidence to the contrary. See MPEP 2112.

Furthermore, assuming arguendo that Hanes's porosity, pore size, and shell thickness are not the same as instantly claimed, the manipulation of these parameters is considered prima facie

obvious to one of ordinary skill in the art since Hanes provides the guidance in which the various factors can be manipulated (column 9 and examples) to yield the desired property. For instance, Hanes teaches manipulating the outlet and inlet temperature when making the particles to manipulate the porosity. Further, Hanes teaches the manipulation of surface roughness (porosity), diameter, and tap density, determine the delivery site of the particles in the lungs (lower lung region or upper lung region). (col. 8, lines 19-68 and column 9). Therefore, a skilled artisan would have been motivated to look at the guidance of Hanes and manipulate the above factors and fabricate the microstructure according to the lung region to be targeted.

Response to Arguments

Applicant argues that both Hanes and Unger does not teach a mean diameter of less than 5 microns. Applicant argues Hanes prefers particles with a size of at least 5 microns. Applicant argues that the instant claims are directed to discrete particulate microstructures that have decreased aggregation and Unger teaches cations such as calcium causes aggregation of phospholipids vesicles. Applicant argues that such an aggregation teaches away from the instantly claimed inhaleable powder composition comprising a plurality of discrete particulate microstructures that are substantially not aggregated in the powder. Applicant argues that column 1, line 50 to column 2, line 9 supports applicant's assertion that calcium causes aggregation and fusion and thus one would not have been motivated to look to Unger. Applicant argues that the examiner's cited passages support applicant's position.

Applicant's arguments filed 12/6/06 have been fully considered but they are not persuasive. Firstly, the directs applicant's attention to claim 1 of US 5,855,913, which claims a particle with **a tap density of less than 0.4g/cm3; a mean diameter between 5 to 30 microns,**

and a aerodynamic diameter between 1 to 3 microns. Also note column 9, lines 40-47, which teaches "maximal deposition…in the alveolar region of the human lung (~60%) occurs for an aerodynamic diameter of approximately d_{aer}=3μm." Hanes does teach a particle size with a **geometric diameter** of 5 to 30 microns but this is not the same as aerodynamic diameter. Applicant has mistaken Hanes' teachings regarding the geometric diameter with aerodynamic diameter, which are different.

Unger teaches on column 68, lines 1-6 that the vesicles preferably have diameters of less than about 30 microns and more preferably less than about 12 microns (note this refers to the geometric diameter). Further, Unger teaches the vesicles for inhalation from dry powder inhalers. The instant specification discloses that a size greater than 50 microns tends to aggregate and clog the valve or orifice of the inhaler. Thus, clearly a problem of clogging the valve of an inhaler is not encountered since Unger teaches the same particle size as claimed.

Secondly, the examiner notes column 1, beginning at line 50 to column 2, line 9; however this passage refers to the *prior art*. Unger clearly teaches, "The present invention is directed to, among other things, the development of new and improved drug and contrast media delivery systems that overcome the problems associated with the prior art." Unger teaches the use of the polymer bound to the lipid overcomes the prior art problems, which will be discussed below.

Further as noted by applicant, Unger teaches calcium and magnesium in the "external environment" of phospholipids vesicles causes the structures to aggregate into larger, multilamellar structures to promote fusion. However, Unger invention is directed to the calcium ions as part of the structural matrix, i.e. part of the vesicle itself, and not part of the *external* environment. Thus, this property of calcium to promote fusion as used by Unger is utilized to

"fuse" the lipid components to form a stable vesicle. Unger's teachings are not directed to placing the formed particles in a solution or "environment" containing calcium, which would cause the aggregation of the individual lipid vesicles. As taught and discussed by Unger on column 1 and 2, during storage the drug tends to leak out the liposomes and thus Unger uses the calcium ion to promote fusion of the lipid components within the vesicle itself.

Applicant argues that the examiner has used hindsight and Hanes teaches away from the aggregation of vesicles.

The examiner acknowledges that Hanes teaches away from aggregation of the *individual* vesicles. Thus, one would not have been motivated to have calcium in the external environment, which would cause the individual vesicles to clump. Hanes also teaches the use of a surfactant to coat the particle to prevent clumping between vesicles. However, Unger teaches and uses the invention pertains to calcium *within* the particle matrix to enforce and stabilize the individual vesicle itself.

On column 10, lines 33-50m Unger teaches:

> Without intending to be bound by any theory of the invention, in the compositions of the present invention, the counter ions (calcium) form salt bridges which crosslink the charged lipids to form aggregates or multilamellar vesicles. The aggregates or multilamellar vesicles may be referred to as cochleates, which may be in the form of a tubule or a spiral. The crosslinking of the counter ions may be noncovalent and may generally be considered an ionic or electrostatic interaction. The lipid covalently bonded to the polymer stabilizes the compositions so that they from **well-defined vesicles**. If the lipid covalently bonded to the polymer is not used in the compositions of the present invention, the counter ions cause the charged lipid species to form amorphous lipid clumps. In many cases, the lipid clumps may take the form of, for example, condensed lipid bilayers, but the lipid clumps do not form stable vesicles with size distributions suitable, for example, for intravenous injection.
>
> The lipid covalently bonded to a polymer (e.g., DPPE-PEG-5,000) causes compaction of the size of the composition in the presence of a counter ion, such as Ca.sup.2+ (FIGS. 2B, 3B and 4B), when compared to the corresponding compositions that do not contain a counter ion (FIGS. 2A, 3A and 4A).

Further, from the above disclosure, it is noted that 1) the term "aggregate" as used by Unger means group of lipids to *form* multilamellar vesicle or liposome; 2) Unger's particles

discrete particles; and 3) Unger utilizes a polymer which is bound to the lipid bound to prevent the problems typically associated with calcium as discussed by Unger in columns 1 to 2. Specifically, Unger uses DPPE-PEG. Thus, Unger clearly teaches an improvement of the prior art vesicles. Hanes also utilizes a lipid conjugated to a polymer, i.e. DPPC-PEG. Thus, the motivation to further utilize a cation such as calcium is to provide stability to the vesicle and promote fusion of the individual lipids within the particle.

The examiner further points to column 4, lines 45-54 to further differentiate applicant's use of the term "aggregate" and Unger's use of the term aggregate:

> "Liposome" refers to a generally spherical or spheroidal cluster or aggregate of amphipathic compounds, including lipid compounds, typically in the form of one or more concentric layers, for example, monolayers, bilayers or multi-layers. They may also be referred to herein as lipid vesicles. The liposomes may be formulated, for example, from ionic lipids and/or non-ionic lipids. Liposomes formulated from non-ionic lipids may be referred to as niosomes. Liposomes formulated, at least in part, from cationic lipids or anionic lipids may be referred to as cochleates.

It is emphasized that Unger utilizes the term to refer to a collection of lipid compounds that form (aggregate) a multilamellar vesicles or liposome and not to define it as collection of particles clumped together. Summarily, the aggregation caused by calcium refers to calcium promoting fusion of the individual phospholipids to form a vesicles rather than fusion *between* the vesicles. Further note Figure 1A which demonstrates calcium's role in forming vesicles.

Applicant argues that Hanes teaches dissolving the polymer in an organic solvent and suspended in an aqueous medium comprising a surface-active agent to form an emulsion, which is followed by evaporating the solvent to form the particles. Applicant argues that the addition of calcium for aggregation purposes might form particles larger than described by Hanes.

Firstly, the examiner points to column 64 of Unger wherein Unger also teaches the use of solvent evaporation to form particles. Further, both references teaches the method of making the

particles is not critical and teaches different methods of making the particles. Secondly, Unger also teaches the use of surfactants (surface active agents) as stabilizing agents to reduce surface tension and both Hanes and Unger teach PEG-phospholipid based particles. Lastly, both Hanes and Unger teaches the similar particle size for inhalation as discussed above. Thus, the use of calcium in Hanes's particles would also have the same effect as taught by Unger, i.e. to promote fusion *between* the individual phospholipids to form a well-defined vesicle. Applicant has not addressed this.

Applicant argues that the limitation that the phospholipid comprises a gel to crystal transition temperature of greater than 40 degrees Celsius is not disclosed.

With regard to the limitation of claim 40, the examiner points out that Hanes teaches the same phospholipids and this limitation is an inherent feature of the claimed phospholipids. Thus, the prior art need not recognize every inherent property of an element to read on the claim. Further, the examiner provides US 5,776,488 as art of interest wherein Mori et al discloses DPPC has a transition temperature of 42 degrees Celsius. See column 3, lines 40-45. Applicant has not addressed this.

Claim 51-52 under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Unger (6,120,751) in further view of Igarashi et al (4201774).

The detailed teaching of Hanes and Unger have been set forth above. Hanes et al teach dry powder inhaler compositions. Hanes teaches several active agents including antibiotics in the composition. Unger teaches the use of calcium to stabilize the phospholipids.

Hanes does not teach the specific use of aminoglycoside antibiotic:

Igarashi et al teaches aminoglycoside antibiotics for the treatment of gram-positive and gram-negative bacteria.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the instant medicament in Hanes et al's composition. One would be motivated to do so since the instant antibiotics treats gram-positive and gram-negative bacteria and depending on the patient's requirement, the appropriate drug is used. One would have expected similar results since Hanes teaches the suitability of antibiotics as the active agent. Therefore, the selection of a particular drug for use in the composition is considered prima facie obvious since the selection depends on the symptoms and disease being treated.

Response to Arguments

Applicant argues that Hanes does not teach calcium or the instant active agent. Applicant argues Unger teaches calcium causes aggregation and the instant specification teaches away from aggregation. Applicant argues Igarashi does not teach particulate microstructures comprising calcium, lipids, and an active agent. Thus, applicant argues the rejection is improper.

Applicant's arguments filed 12/6/06 have been fully considered but they are not persuasive. The teachings of Hanes and Unger have been discussed above. The examiner notes that Igarashi does not teach the instant microstructures; however the examiner points out that Igarashi is not relied for its teaching of the microstructure since the combination of Hanes and Unger are not deficient in this sense. Igarashi teaches the use of the instant active agent for treating gram positive and gram-negative infections. Thus as set forth in the rejection, a skilled artisan would have been motivated to utilize the instant drug to treat a gram positive or negative bacterial infection.

Claims 53-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Unger (6,120,751) in further view of Benson et al (5,006,343).

The detailed teaching of Hanes and Unger have been set forth above. Hanes et al teach dry powder inhaler compositions. Hanes teaches several active agents including antibiotics in the composition. Unger teaches the use of calcium to stabilize the phospholipids.

Hanes does not teach the specific use of fungicides.

Benson et al teach pulmonary administration of active agents to treat pulmonary diseases. Suitable drugs that may be administered for lung specific disease include fungicides. See column 10, lines 33-45.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a fungicide in Hanes et al's composition. One would be motivated to do so since Benson et al teach the use of array of medications including fungicides that are useful for treating lung diseases. Therefore, the selection of a particular drug for use in the composition is considered prima facie obvious since the selection depends on the symptoms and disease being treated.

Response to Arguments

Applicant argues that Hanes does not teach calcium or the instant active agent. Applicant argues Unger teaches calcium causes aggregation and the instant specification teaches away from aggregation. Applicant argues Benson does not teach particulate microstructures comprising calcium, lipids, and an active agent. Thus, applicant argues the rejection is improper.

Applicant's arguments filed 12/6/06 have been fully considered but they are not persuasive. The teachings of Hanes and Unger have been discussed above. The examiner notes

that Benson does not teach the instant microstructures; however the examiner points out that Benson is not relied for its teaching of the microstructure since the combination of Hanes and Unger are not deficient in this sense. Benson teaches the use of the instant active agent for treating lung diseases. Thus as set forth in the rejection, a skilled artisan would have been motivated to utilize the instant drug to treat a certain lung diseases.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 4-15, 18-23, 39-40, 42-47, and 49-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-7, 9-10, 46-50, 54-57, 59, 61-67, 69-70, 74-77, 79-90 of copending Application No. 09/568818. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder

composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antifungals, insulin, etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

Copending independent claims 46, 59, and 82 are directed to a microparticle comprising an active agent and a metal-ion complex with a density as measured by He displacement is 0.5-2 g/ml. Calcium is one of the metal ion species claimed in a dependent claim. Dependent claims are directed to phospholipids and specifically selected from the group comprising "dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, and dimyristylphosphatidylcholine". Dependent claims are directed to the same active agents as claimed in instant application. Dependent claims are directed to an aerodynamic particle size of 0.5-7 microns. Dependent claims are directed to dry powder. Dependent claim are directed to a zwitterionic lipid.

The instant application and '818 are different in that firstly '818 independent claims do not recite a phospholipid; however the dependent claims further comprise phospholipids, more specifically, the instant phospholipids. Thus, the instant application and copending application have overlapping subject matter wherein both application are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion. Secondly, '818 is directed to the broad scope of the metal ion and the instant application is

directed to the metal ion species calcium; however, '818 claims calcium in the dependent claims. Further, '818 is broadly directed to microparticles without claiming the density, the geometric diameter, pore size, etc.; however '818 encompasses the scope of the instant microstructures and the respective properties, which is the narrower scope. Lastly, it should be noted with regard to instant claim 40, although '818 does not specifically claim "phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius", '818 does claim DPPC in the dependent claims and DPPC has a temperature of 42 degrees Celsius.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 4-15, 18-23, 39-40, 42-47, and 49-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 8-9, 11-15, 17, 19-25, 29-32, 53-55, 57-62, 64-66, 67-89 of copending Application No. 09/851226. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antineoplastics, antifungals, specifically insulin,

growth factors etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

'226 is directed to a particulate composition comprising an active agent, a saturated phospholipid, and a polyvalent cation, wherein the ratio of the polyvalent cation to phospholipid is at least 0.05 and is sufficient high to increase the gel-to-liquid crystal transition temperature of the particles without the cation. Dependent claims are directed to calcium as the metal ion. Dependent claim is directed to a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to the same active agent insulin and growth hormones. Dependent claims are directed to a mass median diameter of 0.5-5 microns, an aerodynamic diameter of 0.5-5 microns, and a bulk density of less than 0.5 and 0.05 respectively. The phospholipid is selected from dipalmitoylphosphatidylcholine and disteroylphosphatidylcholine.

The instant application and '226 are different in that '226 is directed to the broad scope of the metal ion and the instant application is directed to the metal ion species calcium; however, '226 claims calcium in the dependent claims. Further, '226 claims the amount of the cation to increase the gel to liquid transition temperature and the instant application does not recite any concentration of the cation. However, the manipulation of concentrations are considered to be prima facie obvious. See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Thus, the instant application and copending application have overlapping subject matter wherein both application are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 4-15, 18-23, 39-40, 42-47, and 49-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15, 19-22, 37-49, 52-64, 67-79, 82-83, 94, and 102 of copending Application No. 10/750934. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antineoplastics, antifungals, specifically insulin, growth factors etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

'934 is directed to a pharmaceutical composition comprising particles comprising an active ingredient in a lipid matrix. The particles have a geometric diameter of less than 3 microns and a mass median diameter of less than 20 microns. Dependent claims are directed to a lipid selected from dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine,

dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine. Dependent claims are directed to hollow, porous particles with a bulk density of less than 0.5 g/cm3, 0.3 g/cm3, and 0.2 g/cm3. Dependent claims are directed to the particle further comprising a polyvalent cation and the specification defines the polyvalent cation as calcium, magnesium, and iron. Independent claim is directed to a specific active agent, amphotericin.

Copending application and instant application are different because '934's independent claim is not directed to a metal ion. However, the independent claims have comprising language and the dependent claim is directed to the particle further comprising polyvalent metal ions. Thus, the combination of a polyvalent ion, phospholipid, and active agent renders a scope that encompasses the scope of the instant application. Thus, both application are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion.

Claims 4-15, 18-23, 39-40, 42-47, and 49-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27, 32-39 of copending Application No. 10/982191. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature

of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antineoplastics, antifungals, specifically insulin, growth factors etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

'191 is directed to a pharmaceutical composition comprising active ingredient and a lipid wherein the gel to liquid crystal transition temperature of greater than 57 degrees Celsius. The dependent claims are directed to the lipid components selected from dipalmitoylphosphatidylcholine. Dependent claims further comprises a divalent cation, specifically calcium. Dependent claims are directed to composition in a dry powder form wherein the particles are hollow and porous particles. Dependent claims are directed to the particles having a geometric diameter of less than 20 microns. Dependent claims are directed to the particles with a bulk density of less than 0.5 g/cm3, 0.3 g/cm3, and 0.2 g/cm3.

Copending application and instant application are different since '934's independent claim is not directed to a metal ion. However, the independent claims have comprising language and the dependent claim is directed to the particle further comprising polyvalent metal ions, specifically calcium ions. Thus, the combination of a polyvalent ion, phospholipid, and active agent renders a scope that encompasses the scope of the instant application. Thus, both application are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion.

Response to Arguments

Applicant states that the rejections will be addressed upon indication of allowable subject matter. Therefore, the rejection s are maintained for the reasons stated above.

Pertinent Prior Art

PGPUB 20020052310 with an effective filing date of 12/29/00 and claiming benefit to US provisional 60/05004 filed 9/15/97 is considered pertinent to applicant's disclosure but does not constitute prior art since the pertinent subject matter regarding divalent cations in section [0093] is not supported in the provisional application of 60/05004. The subject matter claimed in the instant application is supported in US provisional application 60/060337 which has a filing date of 9/29/97.

Conclusion

All the claims are rejected at this time

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharmila S. Gollamudi whose telephone number is 571-272-0614. The examiner can normally be reached on M-F (8:00-5:30), alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1616